REMARKS

In view of these comments and the foregoing claim revisions, applicants request reconsideration of the present application.

I. Status of the Claims

Claims 1 and 2 are revised presently, with support found throughout the specification, *e.g.*, in Table 1 on page 16. No claims are canceled or added. Upon entry of this paper, therefore, claims 1-3, 5, 8, and 9 will be pending and under active consideration.

II. Rejections Withdrawn

Applicants gratefully acknowledge the examiner's withdrawal of objections to the abstract and of Section 103 rejections based on Wong/Okamoto and Wong/Okamoto/Waki.

Applicants note that the only remaining issue is an obviousness rejection.

III. Obviousness Rejection- Waki in view of Okamoto

The pending claims remain rejected over the combination of Waki *et al.*, *Am. J. Pathology* 161: 399-403 (2002), with Okamoto *et al.*, *Proc. Nat'l Acad. Sci. USA* 94: 5367-71 (1997). The Office acknowledges that "Waki does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells" (Office action, page 5). Additionally, the Office also acknowledges that "Waki does not teach a method wherein the normal tissue is normal peripheral blood" (*id.*). Furthermore, the Office acknowledges that "Waki **only** teaches that detection of hMLH1 methylation in **non neoplastic gastric epithelia** may be useful for screening patients who may be at risk of developing **gastric cancer**" (advisory action at page 2; emphasis added).

A. Amendments to the Claims Render Rejection Moot

When determining whether a claim is obvious within the meaning of Section 103, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003), *citing In*

re Royka, 490 F.2d 981, 985 (CCPA 1974). Moreover, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), *quoting with approval In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added). The failure of an asserted combination at least to suggest each and every feature of a claim is fatal to an obviousness rejection. For instance, see MPEP § 2143.03.

With principles and the examiner's acknowledgements in mind, applicants have sought to advance prosecution, without acquiescing to the propriety of the present rejection, by amending the claims to prescribe particular cancers, *exclusive of gastric cancer*, as the focus of the claimed assay. Accordingly, given the examiner's view that "Waki only teaches ... detection of hMLH1 methylation in **non neoplastic gastric epithelia**," for gauging risk of developing **gastric cancer**," it necessarily follows that Waki does not implicate every element of the claims, warranting withdrawal of the rejection.

B. Waki Teaches Away from the Claimed Invention

Furthermore, Waki actually teaches away from the claimed invention. Looking to Table 1 of Waki and the hMLH1 gene, Waki shows **not a hint of methylation** in brain tumor, liver cancer, rectal cancer, lung cancer, pancreatic cancer, ovarian cancer, malignant lymphoma or colon cancer. These data go opposite to applicants' theory. In particular, applicants' data show that there is an inborn methylation status present in subjects who will exhibit cancer later in life. Thus, those subjects who get cancer later in life would exhibit an increased methylation pattern in healthy tissue. In contrast, the artisan looking to Waki's table 1, would come to the opposite conclusion when looking at brain tumors, liver cancer, rectal cancer, pancreatic cancer, ovarian cancer, malignant lymphoma or colon cancer. This is because Waki's table 1 shows no methylation of hMLH1 in patients with these types of cancer.

Absent hindsight informed by applicants' invention, therefore, the skilled artisan could not have intuited how or even whether to predict risk of cancer from the results shown in Table 1. To the contrary, Waki's samples that were taken from tumor tissue -- Table 1 focuses on hMLH1

methylation status in brain, liver, rectal, lung, pancreatic, ovarian lymphoma, lung, and colon tissue -- did not exhibit methylation.

Again, these observations would have led the skilled artisan away from the claimed invention. Exacerbating this teaching-away impact of Waki, vis-à-vis the person of ordinary skill, is the fact that Waki also lacks the sort of negative control that, in principle, might have prompted the skilled artisan to pursue an approach akin to applicants'. That is, Waki omits any case where epimutation was lacking and the patient did not develop cancer. Waki also shows no case where there was epimutation in a healthy individual who later developed cancer.

C. The Office Improperly Combines Okamoto With Waki

The Office specifically states that "Okaomoto is relied on **only** to establish that it was known in the prior art how to **quantitatively determine the frequency of epimutation** of a particular gene in a population of cells." Advisory action, page 2, and Final Office action, page 9.

Yet, the Office then relies on Okamoto for a purpose completely different from showing quantitative epimutation frequency-determination methodology in the prior art. That is, the Office relies on Okamoto for teaching "a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of a Wilms tumor patient to determine if aberrant methylation of H19 was present in normal tissues. As such, Okamoto teaches a method wherein ***epimutation is detected in normal tissue*** (i.e. the peripheral blood)." Advisory action, page 2 (italics added). Thus, the Office shifts from an emphasis on prior knowledge of particular methodology to citing Okamoto for appreciation in the art of the significance of a particular phenomenon, namely, detection of "epimutation ... in normal tissue."

As applicants have underscored previously, however, the skilled artisan would not have combined (and actually would have been dissuaded from combining) Okamoto with Waki in relation to detecting epimutation in "normal" tissue. For instance, see the exposition in applicants' response dated September 8, 2010, at pages 9 and 10, *the factual bases for which the Office has never contradicted.*

In particular, applicants emphasized that the claimed invention explicitly excludes parent of origin-specific genes. This is so because, although imprinted genes normally are subject to epigenetic silencing, a "tumor suppressor gene" as presently recited ***never*** is normally subject to epigenetic silencing. Loss of imprinting is an aberration of a normal process of epigenetic silencing, while silencing of a tumor suppressor is always abnormal.

Faced with these points heretofore, however, the Office has demurred on the ground that Okamoto is invoked only "to teach quantitatively determining the frequency of epimutation of a particular gene in said population of cells and method wherein the normal tissue is normal peripheral blood." It is true that both Waki and Okamoto address epimutation phenomena. Yet, the Office has taken Okamoto completely out of proper context, a factual error that has obscured a fundamental distinction between the epimutation phenomenon addressed in Okamoto, which affected a parent of origin-specific gene, and that epimutation that was Waki's focus, which affected a gene that is <u>not</u> parent of origin-specific. So informed, one of ordinary skill in the art would have readily appreciated that Waki cannot be combined with Okamoto in the manner posited by the examiner here.

In order to establish a case for obviousness based on multiple references, the Office must identify a reason, implicated in the prior art, that would have prompted the person of ordinary skill to combine the elements allegedly drawn from that art. As the U.S. Supreme Court stated *KSR*, cited above, the Office must look to (i) interrelated teachings of the cited reference, (ii) the effects of demands known to the design community or present in the marketplace, and (iii) the background knowledge possessed by a person having ordinary skill in the art, all to the ends of determining whether there was an apparent reason to combine the known element in the fashion claimed by the patent at issue.

Against this background of governing precedent, the Office has combined (1) Waki, directed to non-neoplastic gastric epithelia (**not a parent of origin-specific gene**), and (2) Okamoto, directed to Wilms tumor (**a parent of origin-specific gene**). None of the *KSR* considerations (i) – (iii), *supra*, could have justified this "apples-versus-oranges" conflation of teachings. Parent of origin-specific genes, which are excluded from the present claims, are subject to genomic imprinting whereby, as discussed above, gene expression is dependent on the sex of the parent whence the gene was inherited. This parental bias would have confounded any

notion by the skilled artisan to gauge cancer risk by reference to the methylation status of a parent of origin-specific gene.

For the same reasons, the posited combination of Waki and Okamoto would not have occurred to the skilled artisan. Pursuant to *KSR* and MPEP § 2143.01 (VI), therefore, the combination of Waki with Okamoto is impermissible as a matter of law under section 103, which also justifies a withdrawal of the remaining obviousness rejection.

For at least these reasons, applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSIONS

In view of the foregoing, applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Shaw is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

Respectfully submitted,

Date April 5, 2011

By /Stephen A. Bent/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicants
Registration No. 29,768

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of the relevant fee(s) from the deposit account.